UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P O Box 1450
Alexandria, Virginia 22313-1450
www uspto gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,558	07/31/2006	Udi Damari	27367U	8968

20529 7590 12/01/2009
THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
12/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/575,558	Applicant(s) DAMARI ET AL.	
	Examiner ALLISON M. FORD	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _31 August 2009_.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _90-111_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _90-111_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _20090831_.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

The response of 8/31/2009 has been received and entered into the application file. Claims 1-89 have been cancelled; claims 90-111 have been added as new. All claims have been considered on the merits.

Specification

The amendment to the specification submitted 8/31/2009 has received and entered into the application file.

Oath/Declaration

The supplemental application data sheet (ADS), received 8/31/2009, has been entered into the application file. The supplemental ADS is acceptable under 37 CFR 1.76, and satisfies the requirements under 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statement (IDS) submitted 8/31/2009 has been received and entered into the application file. All references cited therein have been considered, an initialed copy of the IDS is being furnished with this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Cancellation of claims 52-89 renders the rejections under 35 USC 112, second paragraph, thereto, moot.

New Grounds of Rejection:

Presentation of new claims 90-111 has necessitated the following new grounds of rejection:

Claims 93, 94 and 97-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 93 requires the cooling step of claim 90 to comprise controlled initiation of seeding of freezing. Claim 93 is held as indefinite because it is unclear what 'controlled initiation of seeding of freezing' means; the specification refers to a step of *initiating seeding* by contacting the device with cotton wool soaked with liquid nitrogen, it is not clear these steps are one and the same. It would be remedial to amend claim 93 to require the cooling to comprise *controllably initiating seeding*, or the like.

Claim 94 depends indirectly from claim 91, claim 91 defines the cooling rate as being between 0.01°C/min to 3°C/min; claim 94 is held to be indefinite because it inappropriately broadens the range defined by claim 91. Specifically, claim 94 states the cooling is achieved by moving the cartilage along a temperature gradient at a velocity between 0.002 mm/sec and 5 mm/sec, at a cooling rate of between 0.1°C/mm and 50°C/mm; however, these rates equate to:

(Velocity) X	(Cooling rate/mm) X	(Cooling rate/sec) X	(60 sec/min) =	Cooling rate/min
0.002 mm/sec	0.1 °C/mm	0.0002 °C/sec	60	0.012 °C/min
0.002 mm/sec	50 °C/mm	0.1 °C/sec	60	6 °C/min
5 mm/sec	0.1 °C/mm	0.5 °C/sec	60	30 °C/min
5 mm/sec	50 °C/mm	250 °C/sec	60	1,250 °C/min

As shown above, the parameters recited in claim 94 result in cooling rates much greater than those permitted by parent claim 91.

In claim 97 the term "at least about [the glass transition temperature]" (see line 8 of the claim) renders the claim indefinite. The claims recite the limitation "at least about." The term "at least" delineates only numerical values more than the recited value (in the instant case: the glass transition temperature) where the term "about" may be less than or more than the recited value. Because of the conflict of terms, it is unclear which term is limiting. See also MPEP 2173.05(b) (citing Amgen v. Chugai, 18 USPQ2d 1016 (Fed. Cir. 1991), in which the phrase "at least about" was held indefinite). Claims 98-106 inherit this deficiency, and thus are rejected on the same basis.

Each of claims 98-102 and 104, which each depend directly or indirectly on claim 97, are held indefinite because each claim further defines the warming rate, but it is unclear *which* warming rate is being further defined, as claim 97 has two warming steps (b) and (c). Clarification is required.

Additionally, claim 104 also defines "the temperature" as being 0°C or more, however it is unclear if 'the temperature' is referring to the temperature of the environment, or the melting temperature of the cryopreservation solution.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Cancellation of claims 52, 54-56, 68 and 72-75 renders the rejection thereof under 35 USC 102(b) over Schachar et al moot. However, Applicants have presented arguments as to why Schachar et al is not anticipatory of any new claims 90-96 or 111. For completeness, each of Applicants' arguments will be briefly addressed:

First, Applicants assert that new claims 90-95 and 111 require a step of transferring the receptacle to storage at a temperature equal to or below -130 °C, whereas Schachar et al only disclose storing the cartilage at a temperature of -80 °C.

In response, this argument is found persuasive. Schachar et al does not disclose storing the cartilage-containing receptacle at the claimed temperature; therefore no new ground of rejection is made over new claims 90-95 or 111 under 35 USC 102(b) over Schachar et al.

Second, Applicants assert that Schachar et al do not teach or suggest directional cooling as currently claimed.

In response, it is respectfully submitted that only claims 91, 94 and 95 require the cooling to be carried out by movement along one or more consecutive temperature gradients (which is interpreted to be 'directional cooling'). Thus, claims 90, 92, 93 and 111 are not limited to directional cooling, but rather may include any cooling step, including controllably lowering the temperature of the environment in which the cartilage is contained (i.e. as in the method of Schachar et al, where the cartilage is placed in a programmable freezing chamber and the temperature lowered to -40°C at a rate of -1 °C/min). While this specific argument is not found persuasive, the rejection under 35 USC 102(b) is not maintained on the basis that Schachar et al does not teach storing the cartilage at a temperature of less than -130 °C.

Third, Applicants assert Schachar et al does not teach or suggest more than 50[%] chondrocyte recovery upon thawing, but rather the method of Schachar et al results in 50% recovery of chondrocytes.

Applicants assert the instant invention unexpectedly yields greater than 50% recovery of viable chondrocytes upon thawing, as evidenced by the results presented in Table 1 in the specification.

In response, it appears that Applicants are arguing that the instant claims require greater than 50% viable chondrocytes upon thawing, and thus the 50% reported by Schachar et al does not satisfy this limitation. However, it is respectfully submitted that Schachar et al report that the 50% chondrocyte viability rate upon thawing was an average (See Schachar et al, Pg. 916, "Discussion" first paragraph), thus some experiments yielded great than 50% viable chondrocytes, some yielded less. From Figure 5 (at Pg. 916), while no exact values are disclosed, it appears the "Cryo Allo" group had approximately 220 +/- 20 viable cells per unit area, whereas the "Fresh Auto" group had approximately 430 +/- 100 viable cells per unit area (numbers are approximated by Examiner from the graph); thus, in considering the standard deviations, the cryopreservation method of Schachar et al may be considered to yield greater than 50% viable chondrocytes upon thawing. Again, while this specific argument is not found persuasive, the rejection under 35 USC 102(b) is not maintained on the basis that Schachar et al does not teach storing the cartilage at a temperature of less than -130 °C.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Cancellation of claims 52-56 and 68-75 renders the rejection thereof under 35 USC 103(a) over Schachar et al, in view of Sigma Product Information Sheet for DMSO, moot. However, Applicants have presented arguments as to why neither Schachar et al nor the Sigma Product Information

Sheet, nor the combination of the two, render obvious any new claims 90-96 or 111. For completeness, each of Applicants' arguments will be briefly addressed:

First, Applicants assert that new claims 90-95 and 111 require a step of transferring the receptacle to storage at a temperature equal to or below -130 °C, whereas Schachar et al only disclose storing the cartilage at a temperature of -80 °C. Sigma does not cure this deficiency.

In response, this argument is found persuasive. Schachar et al does not disclose storing the cartilage-containing receptacle at the claimed temperature, nor does Sigma cure such deficiency; therefore the rejection previously of record is not applied to any of new claims 90-111.

Second, Applicants assert new claims 90-95 and 111 are method claims which require an active step of moving the receptacle along one or more consecutive temperature gradients, which Schachar et al does not disclose. Applicants traverse the holding of obviousness on the grounds that substitution of one method (moving the sample along a temperature gradient) for another (reducing the temperature around the stationary sample), to yield the predictable result of controllably lowering the temperature of the sample is without merit. Applicants have pointed to the "Claim Interpretation 'In the Examination Process'" to support their position.

In response, it is reiterated that only claims 91, 94 and 95 require the active step of "moving…", thus this argument is not applicable to new claims 90, 92, 93 or 111, as none of these claims limit the method by which the cooling step is performed.

With regards to new claims 91, 94, and 95, which do require the active 'moving...' step, it is respectfully submitted that Applicants' arguments as to the impropriety of the obviousness rejection are not fully understood. The rejection does acknowledge that Schachar et al does not teach moving the sample along a temperature gradient, but rather achieves the cooling step by controllably reducing the temperature within a programmable freezing chamber; however, the rejection is based on the fact that

substitution of a different means for controllably cooling the sample (i.e. moving the sample along a temperature gradient to achieve the same controlled reduction in temperature) would have been *prima facie* obvious, and would have been expected to yield the same predictable result of controllably cooling the sample. Applicant has discussed the effects of directional cooling (at pages 15-16 of Response), but has failed to provide evidence that the effects achieved by directional cooling are distinct from those achieved by cooling a sample by reducing the temperature of the environment (i.e. in a programmable freezing chamber).

Example 3 of the attached exhibit has been fully considered, but is not found to be relevant. Example 3 deals with inherency within a claimed method, specifically that if a prior art reference teaches the same method, but for a different intended use, or otherwise fails to recite the claimed effect, the effect is nonetheless inherent, and the claim is anticipated. It appears Applicants are asserting that because Schachar et al does not teach the specific step of directional cooling, it cannot be held that greater than 50% chondrocyte viability is inherently retained post-thaw. However, as in the instant case Schachar et al specifically discloses that their method (cryopreservation in the freezing chamber) does result in retention of 50% chondrocyte viability post thaw (See Schachar et al, Pg. 917, "Discussion" first paragraph); therefore the 50% chondrocyte viability retention is not asserted to be an inherent result of the method of Schachar et al, based on identical steps as the instant method, but rather, the 50% chondrocyte viability is a disclosed fact reported by Schachar et al.

However, again, while this specific argument is not found persuasive, the rejection previously of record is not applied to any of new claims 90-111 on the basis that neither Schachar et al nor Sigma teach or suggest storing the cartilage at a temperature of less than -130 °C.

Cancellation of claims 52-89 renders the rejection thereof under 35 USC 103(a) over Pegg et al, in view of Schachar et al, moot. However, Applicants have presented arguments as to why neither

Pegg et al nor Schachar et al, nor the combination of the two, render obvious any new claims 90-111. For completeness, each of Applicants' arguments will be briefly addressed:

First, Applicants incorporate all arguments against Schachar et al in their entirety herein.

It is respectfully submitted that all arguments against Schachar et al have been fully addressed above, and the responses are also incorporated in their entirety herein.

Second, Applicants traverse the holding that it would have been obvious to one having ordinary skill in the art to apply the cryopreservation or warming methods of Pegg et al to tissue types other than arteries because artery segments and cartilage are vastly different tissues that have different functions in the body and thus the skilled artisan would not expect them to behave the same.

In response, it is respectfully submitted that it has not been asserted that arteries and cartilage are the same or even similar tissue types, but rather that the method of Pegg et al would be considered applicable to tissue types other than blood vessels. The rejection has been modified so that only the re-warming procedure of Pegg et al is relied upon. Pegg et al report that slow warming of cryopreserved tissues from below the glass-transition temperature to about -100 °C reduces fractures caused by mechanical stress during rewarming. In reading Pegg et al the artisan of ordinary skill would have had a reasonable expectation of successfully applying the rewarming techniques to tissues other than artery segments, such as cartilage, because Pegg et al specifically state that the two-step rewarming procedure is applicable to other cryopreserved tissues which are often subject to fracture during rapid rewarming (See Pegg et al, Pg. 191, first column, 3rd full paragraph). Cartilage was known to be routinely cryopreserved yet to suffer from fractures during rapid rewarming (See Schachar et al). Therefore, one having ordinary skill in the art would have been motivated to apply the two-step warming technique of Pegg et al to procedures for thawing cryopreserved cartilage (such as Schachar et al); and one would have had

reasonable expectation of success based on the suggestion of Pegg et al regarding applicability to other tissues.

Third, Applicants assert that in Table 4 Pegg et al report their method yields artery segments that have endothelial integrity of less than 50%, specifically 45 +/- 7.3%, thus the method of Pegg et al cannot be considered to teach a cryopreservation method that would result in a cell viability of greater than 50% upon thawing.

In response, it is respectfully submitted that 45 +/- 7.3% reads on 52.3%, which is greater than 50%. The values presented in Table 1 of the instant specification are based on the high end of the standard deviation, thus it is appropriate to take the highest values presented by the prior art, as well.

New Grounds of Rejection:

Presentation of new claims 90-111 has necessitated the following new grounds of rejection:

Claims 90, 93, 96 and 111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schachar et al (J Orthop Res, 1999), in light of Sigma Product Information Sheet for Dimethyl Sulfoxide, and in view of Kushibe et al (Ann Thor Surg, 2001).

Schachar et al disclose a method for generating frozen viable osteochondral dowels comprising:

immersing the osteochondral dowels in DMSO for 30 minutes at 20°C (though Schachar et al do not explicitly disclose providing the osteochondral sample and DMSO 'in a receptacle', it will be readily understood by one of ordinary skill in the art that the sample was necessarily provided in some form of receptacle, as a receptacle is necessary to contain the liquid DMSO, as well as to contain the sample during the cooling procedure; DMSO has a freezing temperature of 18.45°C (See Sigma Product Info Sheet); therefore, by initially providing the osteochondral dowels in DMSO at 20°C [in a receptacle] Schachar et al reads on the claimed step of providing a receptacle containing a viable cartilage in a

cryopreservation solution at a temperature above a freezing temperature of the cryopreservation solution' (claim 90, step (a)));

then cooling the osteochondral dowels to -40°C at a controlled rate of -1°C/min (which reads on the claimed step of cooling the viable cartilage in the cryopreservation solution to a temperature below the freezing temperature of the cryopreservation solution at a rate within the claimed range, thereby generating a frozen viable cartilage in the receptacle' (claim 90, step (b)));

followed by storage at -80°C for up to four weeks (See Schachar et al, Pg. 911, "Allografts").

Schachar et al report that upon thawing, approximately 50% of chondrocytes remained viable (See Schachar et al, Pg. 916, "Membrane Integrity of Chondrocytes" & Fig. 5, Pg. 915).

The osteochondral dowels clearly read on 'osteochondral tissue' (claim 93).

Schachar et al differs from the claimed method in that Schachar et al discloses storing the sample at -80 °C, whereas the claimed method requires transferring the frozen sample (in the receptacle) to storage at a temperature equal to or below -130 °C (claim 90, step (c)), specifically between -130 °C and -196 °C (claim 111).

However, it is submitted that at the time the invention was made the art taught that the rate of intracellular ice recrystallization accelerated as the tissue temperature rose above -130 °C and that nearly all biological tissues can be stored in liquid nitrogen (at -196 °C) for up to 10 years (See Kushibe et al, Pg. 1668). Thus, one having ordinary skill in the art, in performing the method of Schachar et al, would have been motivated to modify the method of Schachar et al so as to store the frozen osteochondral dowels, in the DMSO, in the receptacle, in liquid nitrogen (at a temperature of -196 °C) as opposed to -80 °C for the predictable result of reducing intracellular ice recrystallization, as storage at temperatures below -130 °C was taught to reduce intracellular ice recrystallization. Because the samples were stored for up to four

weeks, one would have been particularly motivated to select storage conditions which would optimize chances of recovery of the cells within the graft; because Kushibe et al teach that storage at temperatures below -130 °C reduce intracellular ice recrystallization, one would have been motivated to store the sample at temperatures below -130 °C. One would have had a reasonable expectation of successfully storing the frozen osteochondral dowels (in the DMSO in the receptacle) in liquid nitrogen at a temperature of -196 °C based on the statement of Kushibe et al that nearly all biological materials can be safely stored in liquid nitrogen for up to 10 years. Therefore, the claimed step of transferring the receptacle to storage at a temperature between -130 °C and -196 °C would have been *prima facie* obvious to one having ordinary skill in the art. (claim 90, step (c) and claim 111).

Schachar et al further differs from the claimed method in that Schachar et al reports that upon thawing the samples contained 50% viable chondrocytes, whereas the instant method requires the method to yield a sample which, upon thawing, comprises *more than* 50% viable chondrocytes.

However, it has been held that a *prima facie* case of obviousness exists where the claimed range and the prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. See *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed Cir. 1985). In the instant case "50%" is sufficiently close to "greater than 50%" such that the resulting products would be considered to have the same properties. Therefore, the method of Schachar et al is considered to render obvious the claimed method in that, upon thawing, the thawed viable cartilage of Schachar et al would be expected to have the same properties as a viable cartilage produced by the method of the instant invention.

Finally, it is further submitted that storage in liquid nitrogen (-196 °C), as suggested above, would yield a cryopreserved osteochondral tissue which reads on the frozen viable cartilage product of claim 96.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 90, 92, 93 and 111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schachar et al (J Orthop Res, 1999), in light of Sigma Product Information Sheet for Dimethyl Sulfoxide, and in view of Kushibe et al (Ann Thor Surg, 2001) and Brockbank (US Patent 5,131,850).

The teachings of Schachar et al, Sigma, and Kushibe et al are set forth above. Briefly, the method of Schachar et al involves freezing an osteochondral sample in a programmable freezing chamber to generate frozen osteochondral samples. It has been held to be *prima facie* obvious to modify the method of Schachar et al to include a step of transferring the frozen sample to storage in liquid nitrogen (at a temperature of -196 °C). The method of Schachar et al has been held to render obvious the method of claims 90, 93 and 111.

The method of Schachar et al further differs from the method of instant claim 92 in that neither Schachar et al nor Kushibe et al disclose a step of initiating seeding.

However, it is submitted that initiating seeding was recognized as a routine step in the cryopreservation arts and thus would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. For example, Brockbank disclose that in cryopreservation procedures (including cryopreservation of cartilaginous tissues) the water to ice phase change is initiated by contacting the cryopreservation solution with a burst of liquid nitrogen, addition of a sterile ice crystal, or by vibration (See Brockbank, col. 4, ln 57-63). Each of the methods disclosed by Brockbank read on a step of controllably initiating seeding (which Applicants call "controlled initiation of seeding of freezing") (claim 92).

One having ordinary skill in the art would have been motivated to controllably initiate seeding in the method of Schachar et al in order to hasten the phase change of the cryoprotectant solution. Initiation of seeding is a routine step used in the art of cryopreservation (as evidenced by Brockbank) and thus one would have had a reasonable expectation of successfully initiating seeding by any known method, particularly contact with a burst of liquid nitrogen, addition of a sterile ice crystal, or vibration, each taught by Brockbank. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 90-95 and 111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schachar et al (J Orthop Res, 1999), in light of Sigma Product Information Sheet for Dimethyl Sulfoxide, in view of Kushibe et al (Ann Thor Surg, 2001) and further in view of Arav (US Patent 5,873,254) .

The teachings of Schachar et al, Sigma, and Kushibe et al are set forth above. Briefly, the method of Schachar et al involves freezing an osteochondral sample in a programmable freezing chamber to generate frozen osteochondral samples. It has been held to be *prima facie* obvious to modify the method of Schachar et al to include a step of transferring the frozen sample to storage in liquid nitrogen (at a temperature of -196 °C). The method of Schachar et al has been held to render obvious the method of claims 90, 93 and 111.

Schachar et al does not teach or suggest cooling the osteochondral samples by moving the receptacle (in which the sample and cryopreservation solution are necessarily stored) along one or more consecutive temperature gradients ranging from a temperature above the freezing temperature [of the cryopreservation solution] to a temperature below the freezing temperature [of the cryopreservation solution].

Arav discloses a directional freezing procedure which involves moving a biological sample along a thermal gradient from a temperature above the freezing point of the sample to a temperature below the freezing point of the sample. The directional freezing procedure provides the improvement over equiaxial (nondirectional, i.e. such as the programmable freezing chamber of Schachar et al) freezing methods in that the directional freezing limits uncontrolled nucleation (which causes damage to cells) to the leading edge of the biological sample, permitting controlled nucleation of freezing (which results in significantly less cell damage) along the length of the sample as it passes through the freeze front (See Arav, col. 5, ln 8-42).

It is submitted that one having ordinary skill in the art would have been motivated to substitute the directional freezing device and procedure of Arav for the freezing by the programmable freezing chamber in the method of Schachar et al, in order to reduce cell damage by ice crystallization during the freezing step.

One would have had a reasonable expectation of successfully freezing the osteochondral dowels of Schachar et al by the directional freezing device of Arav based on the disclosure of Arav that the device is suitable for use with various kinds of biological samples (See Arav, col. 3, ln 47-53). Furthermore, Arav disclose the temperature span of the gradient, as well as the rate of temperature change, and speed at which the sample is moved along the gradient may be selected based on the biological sample being treated (See Arav, col. 5, ln 42-67).

The freezing protocol of Schachar et al is carried out at a rate of -1 °C/min (See Schachar et al, Pg. 911, "Allografts"), Avar teaches their device can achieve a cooling rate of -1 °C/min (See Avar, col. 6, ln 55-57); therefore, one would have had a reasonable expectation that the cooling rate required by Schachar et al may be achieved on a device of Avar (claim 91). The velocity at which the sample is moved would have been routinely optimized based on the size of the device, the size of each individual cooling block, and the differences in temperature between different points in the device; however, Avar

disclose that each of these parameters may be optimized for the intended application, therefore the parameters of claims 94 and 95 may have been routinely met through optimization of the prior art device of Avar.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 97-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schachar et al (J Orthop Res, 1999), in view of Kushibe et al (Ann Thorac Surg, 2001) and Pegg et al (Cryobiology, 1997), and in light of the Sigma Product Information Sheet for Dimethyl Sulfoxide.

Schachar et al disclose a process for cryopreserving osteochondral tissue, as well as thawing and transplanting the osteochondral tissue.

Schachar et al disclose cryopreserving allogeneic osteochondral dowels in DMSO and storing the samples at -80°C for up to four weeks (See Schachar et al, Pg. 911, "Allografts"). Please note that though Schachar et al does not explicitly teach the osteochondral dowels were provided in the DMSO *in a receptacle*, it is submitted that one having ordinary skill in the art would immediately recognize that some form of receptacle would have been utilized to contain the osteochondral dowel and the liquid DMSO solution; thus the cryopreserved samples actually include the osteochondral sample, in cryopreservation solution, in a receptacle.

To thaw the cryopreserved samples, the samples were placed in a warm water bath at 37 °C until the ice melted (at a warming rate of approximately 100 °C/min). The samples were then immersed in 100 mL PBS for 30 minutes at 20 °C to remove DMSO before transplantation (See Schachar et al, Pg. 912, first full paragraph).

Schachar et al report that upon thawing, approximately 50% of chondrocytes remained viable (See Schachar et al, Pg. 916, "Membrane Integrity of Chondrocytes" & Fig. 5, Pg. 915).

Following thawing, the samples were transplanted into cartilage defects in the knee joint, the size and shape of the sample being compatible with that of the defect site (See Schachar et al, pg. 911 "Transplantation").

Schachar et al differs from the method of claims 97-106 in that Schachar et al does not disclose providing the receptacle containing the frozen viable cartilage at an initial temperature below the glass transition temperature of the cryopreservation solution (claim 97, step (a)).

However, as discussed above, though Schachar et al report storing the osteochondral dowel samples at a temperature of -80 °C teachings in the art suggested that storage at temperatures lower than -130 °C reduced the rate of intracellular ice recrystallization (See Kushibe et al, Pg. 1668); therefore, in order to reduce the rate of intracellular ice recrystallization upon thawing one having ordinary skill in the art would have been motivated to modify the method of Schachar et al such that the storage step is carried out at temperatures of less than -130 °C. Kushibe specifically suggest storage in liquid nitrogen (at -196 °C) is effective and safe for storage of nearly all biological tissues for up to 10 years. The method of Schachar et al involves storage for a period of up to four weeks, thus storage in liquid nitrogen would have been expected to be successful and safe for use in the method of Schachar et al. Therefore, in modifying the method of Schachar et al to involve storing the sample in liquid nitrogen at -196 °C, to thaw the sample the osteochondral sample of Schachar et al would necessarily be provided [in the receptacle] at an initial temperature of -196 °C (which is below the glass transition temperature of DMSO, see specification at Pg 6, lines 13-14). (claim 97, step (a)).

Schachar et al further differs from the claimed method in that Schachar et al does not disclose warming the frozen viable osteochondral sample in a two step re-warming process, as defined by claims 97-106.

However, in modifying the method of Schachar et al to include storage at temperatures of -196 °C, and thus provision of the sample for thawing at a temperature of -196 °C, one of ordinary skill in the art would have further been motivated to modify the method by which the sample is thawed because evidence in the art taught that rapid rewarming of tissues from -180°C by immersion in a 37 °C water bath causes significant fractures (See Pegg et al, Pg. 185. Table 1 & Experiment 1).

To reduce the damage caused to tissues upon rewarming from -180 °C Pegg et al suggest a two-step rewarming process, comprising:

a first step of removing the cryopreserved samples from the liquid nitrogen refrigerator and placing it in an insulated outerbag at room temperature (~25°C); during this stage the tissues warm from -180°C to -100°C at an initial rate of 40-60°C/min, slowing to 15-17°C/min as the temperature approached -100°C (which reads on the claimed step of warming the receptacle containing the frozen viable cartilage and the cryopreservation solution from the initial temperature (-196 °C) to an intermediate temperature which is above the glass transition temperature but no more than the transition temperature of the cryopreservation solution wherein recrystallization would begin to occur at any point in the cartilage; -100 °C satisfies these limitations according to the specification (See Spec at Pg. 6, ln 13-14 and at Pg. 11, ln 7-12) (claim 97, step (b)); -100 °C is less than -10°C (claim 103); the warming rate of 40-60°C/min also is within the range defined by the specification as being 'sufficiently slow as to minimize fracture of the frozen viable cartilage' (See Spec at Pg. 11, ln 19-20) (claims 98, 99); 40-60 °C/min is considered sufficiently close enough to the claimed rate of 90 °C/min , that one skilled in the art would have expected the rates to have the same effect on the tissue, and thus a holding of obviousness is proper. See *Titanium Metals Corp. of America v. Banner*, id.(claim 100)); then

a second step of rapidly rewarming the sample by submerging the samples in a warm water bath (37°C); during this stage the tissues were allowed to completely thaw at an initial rate of over 2000°C/min, slowing to 50-80°C/min after 15 seconds (which reads on the claimed step of warming the

frozen viable cartilage and the cryopreservation solution from the intermediate temperature (-100 °C) to a temperature that is at least substantially equal to the melting temperature of the cryopreservation solution (in the case of DMSO: 18.45°C), the warming rate of 50-80 °C/min being within the claimed ranges of claims (101 and 102), thus considered to be sufficiently high to minimize recrystallization (claim 97, step (c)) (See Pegg et al, Pg. 187-188 "Experiment 4").

One would have been motivated to substitute the two-step rewarming process of Pegg et al for the standard rapid rewarming procedure of Schachar et al, when the osteochondral samples of Schachar et al are stored at -196 °C, because Pegg et al provides evidence that the two-step rewarming process significantly reduces fractures in the tissues upon thawing (See Pegg et al, Pg. 185, Table 1 & Pg. 188, Table 2). Based on this disclosure in the art that the two-step rewarming technique provided improved results with regards to fracture rates in thawing of cryopreserved tissues, and noting that disclosure of the two-step rewarming procedure evidences that such a technique was part of the ordinary capabilities of one skilled in the art, it is submitted that it would have been obvious to one of ordinary skill in the art to utilize the two-step rewarming technique of Pegg et al in the method of Schachar et al, as modified to include storage in liquid nitrogen, for the predictable result of reducing fractures within the osteochondral samples upon thawing. See *KSR International Co. v Teleflex Inc.* 550 US 398 (US 2007) 82 USPQ2d 1385.

It is further submitted that the second warming step suggested by Pegg et al is identical to the rapid warming step taught by Schachar et al (See Schachar et al, Pg. 912, first full paragraph), which is applied to the samples at -80 °C; thus the modification to the method of Schachar et al would actually only involve adding the first slow warming step, whereby the sample is warmed from the temperature of -196 °C to temperatures of about -100 °C (i.e. -80 °C).

It is unclear if the second warming step of Pegg et al (or the sole warming step of Schachar et al, which is considered to be equivalent to the second warming step of Pegg et al) involves submersion of the

entire receptacle into a 37 °C water bath, or if the frozen sample in the frozen cryopreservation solution is removed from the receptacle in which it was provided, and then submerged in the water bath. However, it is submitted that removal of the frozen sample (along with frozen cryopreservation solution) from the receptacle would have been *prima facie* obvious to one having ordinary skill in the art for the purpose of hastening thawing of the tissue. By removing the sample from the receptacle the skilled artisan would expect to hasten the thaw, as greater surface area of tissue would be exposed to the water bath, and the receptacle would not take heat energy away from the frozen sample. Therefore, removal of the frozen tissue from the receptacle prior to placement in the 37 °C water bath would have been *prima facie* obvious. (claim 104 and 105) Furthermore, with regards to use of a 'pulling member' to remove the sample from the receptacle, it is submitted that any sterile means for recovery of a biological sample, such as cryopreserved and/or thawed cartilage from its holding receptacle, would have been *prima facie* obvious to the artisan of ordinary skill. Due to the extreme temperatures use of laboratory tools would have been recognized as necessary to permit safe (and sterile) recovery of the biological samples. (claim 106)

Schachar et al further differs from the claimed method in that Schachar et al reports that upon thawing the samples contained 50% viable chondrocytes, whereas the instant method requires the method to yield a sample which, upon thawing, comprises *more than* 50% viable chondrocytes.

However, it has been held that a *prima facie* case of obviousness exists where the claimed range and the prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. See *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed Cir. 1985). In the instant case "50%" is sufficiently close to "greater than 50%" such that the resulting products would be considered to have the same properties. Therefore, the method of Schachar et al is considered to render obvious the claimed method in that, upon thawing, the thawed

viable cartilage of Schachar et al would be expected to have the same properties as a viable cartilage produced by the method of the instant invention.

It is further submitted that modification of the method of Schachar et al, as suggested above, would yield a thawed osteochondral tissue which reads on the thawed viable cartilage product of claim 107.

The thawed osteochondral tissue may be routinely transplanted per the method taught by Schachar et al (See Schachar et al, Pg. 911 "Transplantation"). (claims 108-110)

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651